Serum 25-hydroxyvitamin D (25D) falls below 30 ng/mL and serum 1,25-dihydroxyvitamin D (1,25D) becomes undetectable as chronic kidney disease (CKD) progresses. Cholecalciferol or ergocalciferol are widely prescribed but cannot reliably raise 25D and 1,25D and lower elevated parathyroid hormone (PTH). They are replaced/combined with calcitriol (or 1a-25D analog) when PTH inevitably rises, contrary to the current KDIGO guideline. The justification for calcitriol use is that too much renal CYP27B1 has been lost, limiting hormone production. Randomized clinical trials (RCTs) have demonstrated that extended-release calcifediol (ERC) safely and sufficiently raises serum 25D and 1,25D, and effective treatments elevated PTH despite declining estimated glomerular filtration rate (eGFR), but the mechanism is not fully elucidated and requires further investigation.

**Methods**

Changes in serum total 25D and 1,25D, calcifediol (25D3), 24,25-dihydroxyvitamin D3 (24,25D3) and calcitriol (1,25D3) during ERC treatment in four RCTs were assessed compared as a function of eGFR. In one study, 80 non-CKD patients with COVID-19 were treated for 4 weeks (wks) with 300 mcg/day (d) for the first 3 days and 1,25D and lower elevated parathyroid hormone (PTH).

In another, 33 hemodialysis (HD) patients were treated for 26 wks with 900 mcg/wk (Strugnell 2021). In a further three studies (pooled), 285 non-dialysis patients with eGFR of 30.6±0.6 (mean±SE) mL/min/1.73m2 were treated with 210 mcg/wk for 12 weeks, at which time 74% were increased to 420 mcg/wk (Sprague 2016). In another, 33 hemodialysis (HD) patients were treated for 26 wks with 900 mcg/wk (Strugnell 2021).

Baseline eGFR and serum total 25D levels of subjects included in the present analysis are listed in Table 1, along with subject numbers, ERC doses, and treatment durations for each population.

**Subjects**

Baseline eGFR and serum total 25D levels of subjects included in the present analysis are listed in Table 1, along with subject numbers, ERC doses, and treatment durations for each population.

**Results**

- **Mean serum total 25D values at baseline were lower in patients with reduced eGFR (Table 1).**
- **Mean serum 1,25D or total 1,25D values at baseline (circled in Figure 1) were proportional to eGFR.**
- **During ERC treatment, mean serum 25D, or total 25D rose to 870 ng/mL with peak levels proportional to the total administered dose (Figure 1).**
- **Mean serum 1,25D or total 1,25D rose linearly with serum 25D or total 25D at similar rates in all eGFR groups (Figure 1).**
- **However, serum 24,25D levels rose less quickly with rising serum 25D, as eGFR decreased (Figures 2 and 3).**

**Conclusions**

- **ERC reliably raised serum 25D, 1,25D, and total 25D and 1,25D irrespective of eGFR, making it an attractive alternative to calcitriol (or 1a-25D analogs) for treating persistently rising PTH in CKD 3-4.**
- **Declining eGFR does not affect rate of conversion of 25D to 1,25D, indicating the importance of extra-renal conversion in raising serum 1,25D during ERC treatment.**
- **Increases in serum 24,25D were dependent on 25D elevation and limited by declining eGFR, suggesting that this metabolite is not disproportionately increased by ERC and derives primarily from kidney.**

**References**


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